DATA EVALUATION RECORD

FLUTRIAFOL

Study Type: OPPTS 870.4300 [§83-5];
Combined Chronic Toxicity / Carcinogenicity Study in Rats

47363401

Work Assignment No. 5-1-151 G; formerly 4-1-151 G (MRID 47090352)

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Template version 02/06

TXR#: 0054780

DATA EVALUATION RECORD

STUDY TYPE: Combined chronic toxicity/carcinogenicity study in rats (dietary); OPPTS 870.4300 [§83-5]; OECD 453.

PC CODE: 128940 **DP BARCODE:** 340368, 350364

TEST MATERIAL (PURITY): Flutriafol (93% a.i.)

SYNONYMS: α-(2-fluorophenyl)-α-(4-fluorophenyl)-1*H*-1,2,4-triazole-1-ethanol

CITATION: Pigott, G.H. (1986) Flutriafol: 2 year feeding study in rats. Imperial Chemical Industries PLC, Central Toxicology Laboratory, Macclessfield, Cheshire, UK. Laboratory Study No.: PR0542. Laboratory Report No.: CTL/P/1220, May 22, 1986. MRID 47090352. Unpublished.

Pigott, G.H. (1986) Flutriafol: 2 year feeding study in rats. Individual Animal Data Supplement. Imperial Chemical Industries PLC, Central Toxicology Laboratory, Macclessfield, Cheshire, UK. Laboratory Study No.: PR0542. Laboratory Report No.: CTL/P/1220, May 22, 1986. MRID 47363401. Unpublished.

SUBMITTER/SPONSOR: Cheminova, Inc., 1600 Wilson Boulevard, Suite 700, Arlington, VA (originally sponsored by Imperial Chemical Industries PLC)

EXECUTIVE SUMMARY: In a combined chronic toxicity/carcinogenicity study (MRID 47090352, 47363401) 52 Alpk:AP rats/sex/dose were exposed to flutriafol (93% a.i.; Batch No.: P10) for up to 24 months in the diet at concentrations of 0, 20, 200, or 2000 ppm (calculated to be, 0, 1.02, 10.0, and 102 mg/kg bw/day in males; and 0, 1.27, 12.2 and 122 mg/kg bw/day in females). Additionally, 12 rats/sex/dose were treated similarly for up to 12 months.

No treatment-related effects were observed on mortality, ophthalmology, clinical chemistry, or urinalysis.

Grossly, small discolored foci were commonly observed after 2 years of treatment. After 1 year of treatment, an increased incidence of fatty change in the liver was observed in the 200 and 2000 ppm males (21-93% of treated rats vs 7% controls). The severity was minimal in the

controls and 200 ppm males, but was minimal to marked in the 2000 ppm males. After 2 years of treatment of the 200 and 2000 ppm males, increased incidences of minimal to severe hepatic fatty change (54-96% treated vs 24% controls) and clear cell foci of hepatocytes (40-50% treated vs 18% controls) were observed.

At 2000 ppm, systemic toxicity was noted in both sexes as follows. More rats appeared thin and fewer rats had distended abdomens. Final body weights were decreased by 12-22%, and cumulative body weight gains were decreased by 12-48% throughout the study. Weekly food consumption was frequently decreased by 4-24% throughout treatment, and total food consumption was decreased by 8-12% for the Weeks 1-13 interval. Food utilization (g food/g growth) was increased by 8-11% for the Weeks 1-4 interval, and by 7% (each sex) for the Weeks 1-12 interval.

A slight treatment-related anemia was noted in the 2000 ppm group as indicated by the following decreases ($p \leq 0.05$) in hematological parameters: (i) hemoglobin in males (↓4-7%) during Weeks 4-65 and females (↓4-9%) during Weeks 13-52, 78, and 92; (ii) hematocrit in males (↓3-8%) during Weeks 26-65 and females (↓5-11%) during Weeks 13-52, 78, and 104; (iii) mean cell volume in males (↓3-8%) during Weeks 4-104 and females (↓2-10%) during Weeks 4-104; and (iv) mean cell hemoglobin in males (↓4-7%) during Weeks 4, 26, 39, and 78-104 and females (↓4-10%) during Weeks 4-52 and 78-104. The total iron binding capacity of the 2000 ppm females was increased ($p \leq 0.01$) by 40%. Increased ($p \leq 0.05$) lymphocytes were observed in the 2000 ppm females (↑22-61%) during Weeks 26-78 and 104, and increased ($p \leq 0.05$) total leukocytes were noted at Weeks 26, 39, and 78 (↑20-38%). The hematological changes were not considered to be an adverse effect due to the minor decreases in magnitude without corroborating clinical signs.

At 2000 ppm, the following toxicologically significant differences ($p \leq 0.05$) were observed: (i) increased plasma cholesterol in the females throughout the study (↑24-49%; NS at Week 91); (ii) decreased plasma triglycerides in the males during Weeks 4-65 (↓40-68%); (iii) decreased alkaline phosphatase in the males during Weeks 13-91 (↓12-33%); (iv) increased plasma total protein in the females throughout treatment (↑4-9%); and (v) increased plasma alanine transaminase during Weeks 4 and 13 (↑54-82%).

At 2000 ppm, hepatoxicity was noted in both sexes. In both sexes, increased liver weights, both absolute and adjusted for body weight, were observed after 1 year of treatment (incr 11-37%) and after 2 years (incr 27-34%, except similar to control for absolute liver weight of the females). There was hepatic enlargement, often coupled with the presence of numerous discolored foci, commonly observed in both sexes. These liver findings were observed after 2 years of treatment, but not after 1 year of treatment. After 2 years of treatment, the following histological hepatic lesions were increased in incidence in the females: (i) minimal to severe fatty change (65% treated vs 23% controls); (ii) bile duct proliferation/ cholangiolarfibrosis (67% treated vs 44% controls); (iii) hemosiderin accumulation in Kupffer cells (55% treated vs 0% controls); and (iv) centrilobular hypertrophy (8% treated vs 0% controls). Hepatic centrilobular hypertrophy was increased in incidence at the interim sacrifice in males (71%) and females (31%), but only minor increases were noted at terminal sacrifice in both sexes (6-8%) with 0% in the controls. An increased incidence of foci of cortical macrophages in adrenal glands was observed in the 2000

ppm females (80% treated vs 25% controls); however, there was no corroborating evidence of toxicity in the adrenal gland, and this lesion alone was not considered adverse.

The LOAEL is 2000 ppm (102/122mg/kg bw/day in males/females), based on adverse liver effects (increased liver weights, fatty change, bile duct proliferation/cholangiolarfibrosis, hemosiderin accumulation in Kupffer cells and centrilobular hypertrophy), and clinical chemistry findings. The NOAEL is 200 ppm (10.0/12.2 mg/kg bw/day in males/females).

At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls. Dosing was considered adequate based on decreased body weight gain and food consumption, increased food utilization, and hepatotoxicity observed in both sexes.

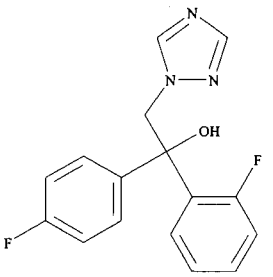
This study is classified as **Acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4300; OECD 453) for a combined chronic toxicity/carcinogenicity study in rats.

COMPLIANCE - Signed and dated GLP Compliance, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Flutriafol

Description:	White powder
Batch #:	P10
Purity (w/w):	93% a.i.
Stability of compound:	Stable in the diet over a 10 week period at room temperature.
CAS #:	76674-21-0
Structure:	

2. Vehicle: Diet

3. Test animals

Species:	Rat
Strain:	Alpk:AP (Wistar-derived)
Age and mean weight at study initiation:	Approximately 37 days old; 130-134 g males; 121-122 g females
Source:	Animal Breeding Unit, Imperial Chemical Industries PLC, Alderley Park, Macclesfield, Cheshire, UK
Housing:	4/sex in suspended, stainless steel, wire mesh cages with solid sides
Diet:	Steam expanded Porton Combined Diet until Week 29-33 (dependent on replicate and group) and then CT1 diet (Special Diets Services, Witham, Essex, UK), *ad libitum*, except during urine collection
Water:	Filtered (0.22 µm) tap water, *ad libitum*, except during urine collection
Environmental conditions	
Temperature:	21±2°C
Humidity:	≥45%
Air changes:	≥15/hr
Photoperiod:	12 hrs light/12 hrs dark
Acclimation period:	6 days

B. STUDY DESIGN

1. In life dates: Start: 11/02/82 End: Approximately 11/02/84 (exact date not provided)

2. Animal assignment: Animals were randomly assigned to the test groups presented in Table 1.

TABLE 1. Study design. [a]

Nominal Dose (ppm)	Dose to animal (mg/kg/day; M/F) [b]	Terminal Sacrifice (24 months; # rats/sex)	Interim Sacrifice (12 months; # rats/sex)
0	0	52	12
20	1	52	12
200	10	52	12
2000	100	52	12

a Data were obtained from page 16 of MRID 47090352.

b Dose to animal estimated by the reviewer by converting the nominal dose (ppm) to mg/kg/day using the conversion factor of 1 ppm = 0.05 mg/kg/day.. Thus, this is an approximate value based on nominal concentrations rather than actual compound intake, which was not reported in the study.

3. **Dose-selection rationale:** Based on the results of a concurrently submitted 90-day oral toxicity study (MRID 47090345) in rats, the doses summarized in Table 1 were selected for the combined chronic toxicity/carcinogenicity study. In a subchronic oral toxicity study flutriafol was administered to 20 Wistar rats/sex/dose in the diet at dose levels of 0, 20, 200, or 2000 ppm for 90 days. At 20 ppm, sporadic decreases ($p<0.05$) in food consumption of 4-12% in was observed in both sexes. At 200 ppm sporadic decreases ($p<0.05$) of 5-10% were noted in food consumption and overall food consumption was decreased by 6-7% in both sexes. Additionally in the females, absolute and adjusted liver weights were increased by 5-8%. Aminopyridine-N-demethylase (APDM) activity was increased by 22-27% in both sexes, and smooth endoplasmic reticulum proliferation in the liver was increased in the males.

   At 2000 ppm, mild anemia was observed at 2000 ppm. Increases in absolute and adjusted for body weight liver weights were observed in both sexes. Increased incidence of hepatocyte vacuolation (fatty change) was noted. Centrilobular hypertrophy, with associated proliferation of smooth endoplasmic reticulum and elevated APDM activity, was also observed in both sexes at this dose. Additionally, triglycerides were decreased, and cholesterol was increased in both sexes. Body weight gains were decreased throughout the study in both sexes. Food consumption and overall (Weeks 1-13) food consumption was decreased in both sexes.

4. **Treatment preparation, analysis, and administration:** Dietary formulations were prepared at approximately 4-week intervals by mixing ground (20 μm nominal) flutriafol with the diet. The dietary formulations were stored in jars at room temperature until use. Samples of all dose formulations were taken from the first batch of diet prepared and at approximately 4-week intervals thereafter for concentration analyses. Additionally, samples were collected from 4 different sampling points in the mixer and in the storage jars, and homogeneity was determined. The stability of flutriafol in powdered diet was established over a nine week period at room temperature in a previous study, which was submitted concurrently (MRID 47090344).

Results

Homogeneity (as range of % coefficient of variation): 1.1-8.3%

Stability (% of initial concentration): 95.5-98.0%

Concentration (range as % of nominal):

Dose	Concentration Range (% nominal)
20 ppm	86-110
200 ppm	93-117
2000 ppm	95-105

The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the animals was acceptable. Homogeneity was only marginal in the low dose (8.3% C.V.), but the concentration was <91% nominal in only 1/22 reported concentration measurements.

5. **Statistics:** Statistical differences between control and treated groups were expressed at the 1% or 5% level.

PARAMETER	ANALYSIS CONDUCTED
Body weight gain Food consumption Food utilization Hematology Clinical chemistry Urinalysis	Analysis of variance (ANOVA) was performed to determine differences among groups. 2-sided Student's t-test, based on the error mean square of the analysis, was performed for pair-wise comparisons of each treated group with the control group.
Organ weights	Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) on terminal body weight were used to determine differences among groups 2-sided Student's t-test, based on the error mean square of the analysis, was performed for pair-wise comparisons of each treated group with the control group.
Survival	Kaplan-Meier survival estimate of the survival function was performed. The logrank test was used to compare the survival distributions of each treatment group with the control group.
Blood total iron binding capacity Serum iron concentrations	A 2-sided t-test was performed to compare each treated group mean with the control group mean.
Neoplastic pathology Non-neoplastic pathology	One-sided Fisher's Exact Test was used for pair-wise comparisons of treated groups with the control groups. When the data indicated a possible increasing tumor incidence with dose, these findings were further analyzed using the Armitage test for positive linear trend.

These statistical analyses were considered appropriate. Standard deviations were not reported with the means in the tabulated data. Instead, the approximate 95% confidence limits were reported; however, standard deviations would have been more appropriate.

C. METHODS

1. Observations

a. **Cageside observations**: Animals were observed at least once daily for signs of toxicity and mortality.
b. **Clinical examinations**: Detailed clinical examinations were performed weekly.

c. **Neurological evaluations**: Neurological evaluations were not performed; however, oral acute (MRID 47090408) and subchronic (MRID 47090410) neurotoxicity studies in rats were concurrently submitted.

2. **Body weight**: All rats were weighed prior to initiation of treatment, weekly for the first 13 weeks, then every 2 weeks beginning with Week 16, and at necropsy. Cumulative body weight gains were reported each time the rats were weighed.

3. **Food consumption, food utilization, and compound intake**: Food consumption for each cage was measured each week for the first 13 weeks, Week 16, and every fourth week thereafter. Total food consumption was also reported for Weeks 1-13. Food utilization (g food/g growth) was reported for the intervals Weeks 1-4, 5-8, 9-12, and 1-12. Compound intake was not reported.

4. **Ophthalmoscopic examination**: Twenty rats/sex from each of the control and 2000 ppm dose groups were subjected to ophthalmoscopic examination after approximately 52 and 104 weeks.

5. **Hematology and clinical chemistry**: Blood was collected from 12 rats/sex/dose group for hematology and 12 different rats/sex/dose group for clinical chemistry. Selected animals were replaced if they died, in order to maintain acceptable group sizes. Blood was collected from the tail vein prior to treatment, then after 4 and 13 weeks, and subsequently at 13 week intervals. Blood was collected at termination by cardiac puncture. The following CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count*		Reticulocyte count
	Blood clotting measurements*	X	Total iron binding capacity [a]
	(Thromboplastin time)	X	Serum iron capacity [a]
X	(Kaolin-cephalin time)		
X	(Prothrombin time)		

* Recommended for combined chronic/carcinogenicity studies based on Guideline 870.4300.
a Measured only at termination

b. Clinical chemistry

	ELECTROLYTES		OTHER
	Calcium	X	Albumin*
	Chloride		Creatinine*
	Magnesium	X	Urea nitrogen*
	Phosphorus	X	Total Cholesterol*
	Potassium*		Globulins
	Sodium*	X	Glucose*
	ENZYMES (more than 2 hepatic enzymes eg., *)		Total bilirubin
X	Alkaline phosphatase (ALP)*	X	Total protein (TP)*
	Cholinesterase (ChE)	X	Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		
X	Alanine aminotransferase (ALT/ SGPT)*		
X	Aspartate aminotransferase (AST/ SGOT)*		
	Gamma glutamyl transferase (GGT)*		
	Sorbitol dehydrogenase*		
	Glutamate dehydrogenase*		

* Recommended for combined chronic and carcinogenicity studies based on Guideline 870.4300.

6. **Urinalysis:** Urine was collected from 12 rats/sex/dose group, the same rats designated to be sampled for clinical chemistry analyses. Urine was collected for approximately 18 hours prior to treatment, then after 4 and 13 weeks, and subsequently at 13 week intervals. During urine collection, the selected animals were individually housed in metabolism cages, and the rats were denied access to food and water. The following CHECKED (X) parameters were examined.

	Appearance*	X	Glucose*
	Volume*	X	Ketones
X	Specific gravity / osmolality*		Bilirubin
X	pH*		Blood/ red blood cells*
	Sediment (microscopic)		Nitrate
X	Protein*	X	Urobilinogen

* Recommended for combined chronic and carcinogenicity studies based on Guideline 870.4300.

7. **Sacrifice and pathology:** All animals that died or were sacrificed *in extremis* and those sacrificed on schedule in the main and satellite groups were subjected to gross pathological examination. Animals scheduled for sacrifice at Weeks 53 and 105 were sacrificed by over-exposure to halothane BP vapor, and were exsanguinated. The following CHECKED (X) tissues were collected. Additionally, the (XX) organs were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	X	Aorta, thoracic*	XX	Brain (multiple sections)*+
X	Salivary glands*	X	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	X	Spleen*+	X	Eyes (retina, optic nerve)*
X	Jejunum*	X	Thymus		GLANDULAR
X	Ileum*			XX	Adrenal gland*+
X	Cecum*		UROGENITAL	X	Lacrimal/Harderian gland
X	Colon*	XX	Kidneys*+	X	Parathyroids*
X	Rectum*	X	Urinary bladder*	X	Thyroids*
XX	Liver*+	XX	Testes*+		OTHER
	Gall bladder* (not rat)	X	Epididymides*+	X	Bone
	Bile duct* (rat)	X	Prostate*	X	Skeletal muscle
X	Pancreas*		Coagulating glands	X	Skin*
		X	Seminal vesicle*	X	All gross lesions and masses*
	RESPIRATORY	XX	Ovaries*+		
X	Trachea*	X	Uterus*+		
X	Lung*++	X	Mammary gland* (females)		
X	Nose*	X	Cervix		
	Pharynx*				
X	Larynx*				

* Recommended for combined chronic toxicity/carcinogenicity studies based on Guideline 870.4300
\+ Organ weight required in combined chronic toxicity/carcinogenicity studies
++ Organ weight required if inhalation route

The eyes and Harderian glands were fixed in Davidson's fixative. Skin and testes were fixed in Bouin's solution. All other tissues were fixed in neutral buffered 10% formol saline. Samples were routinely processed and stained with hematoxylin and eosin. All samples were examined, except the Sponsor stated that only representative samples of the nasal passages were examined from a proportion of the control and test rats.

8. **Microbiological sentinels:** Additional animals were used to verify that infection did not compromise this study. Extra animals (24/sex/dose) received 2000 ppm Flutriafol or control diets for 104 weeks and were checked daily for any change in clinical condition. Moribund animals were killed and examined by a microbiologist. The results indicated no evidence of disease or infection which would have compromised the study.

II. RESULTS

A. OBSERVATIONS

1. **Clinical signs of toxicity:** The Sponsor stated that the only treatment-related findings were more rats that appeared thin and fewer rats with distended abdomen in the 2000 ppm group (data not provided). These findings corresponded to the effect on body weight.

2. **Mortality:** No treatment-related effect was observed on mortality. Survival exceeded guideline requirements of 50% at Week 78 and 25% at Week 104.

B. BODY WEIGHT AND BODY WEIGHT GAINS: Final body weights were decreased ($p \leq 0.01$) in the 2000 ppm males (↓12%) and females (↓22%; Table 2). Only the initial and final body weights were reported. Decreased ($p \leq 0.01$) cumulative body weight gains were observed throughout the study in the 2000 ppm males (↓12-48%) and females (↓15-34%). Transient differences in cumulative body weight gains were noted sporadically in the other dose groups, but were not considered adverse.

TABLE 2. Mean body weights and body weight gains (g) at selected intervals in rats treated with flutriafol in the diet for up to 2 years. [a]

Week(s)	Dose (ppm)			
	0	20	200	2000
Males				
Initial body weight	133.5	129.9	132.6	132.0
Final body weight	625.4	621.6	613.4	549.0** (↓12)
BWG (0-1)	49.0	51.7* (↑6)	48.8	25.3** (↓48)
BWG (0-13)	361.8	366.0	359.5	304.1** (↓16)
BWG (0-51)	529.3	529.0	529.7	456.3** (↓14)
BWG (0-63)	543.5	549.7	552.3	476.9** (↓12)
BWG (0-103)	495.2	496.4	481.5 (↓3)	420.3** (↓15)
Females				
Initial body weight	122.1	121.1	122.0	120.6
Final body weight	399.6	393.2	397.3	311.3** (↓22)
BWG (0-3)	79.7	78.3	77.7	67.5** (↓15)
BWG (0-13)	161.4	158.8	153.5** (↓5)	133.3** (↓17)
BWG (0-51)	240.6	233.3	232.3	175.9** (↓27)
BWG (0-93)	298.5	290.6	280.9	198.4** (↓34)
BWG (0-103)	277.0	273.5	279.8	193.4** (↓30)

a Data were obtained from Table 6-7 on pages 49-56 of MRID 47090352. Standard deviations were not reported. Percent difference from controls, calculated by reviewers, is included in parentheses.

** Significantly different ($p \leq 0.01$) from the control groups

C. FOOD CONSUMPTION AND COMPOUND INTAKE

1. **Food consumption:** Food consumption was frequently decreased ($p \leq 0.05$) throughout treatment in the 2000 ppm males (↓4-24%) and females (↓6-23%; Table 3). Total food consumption for the interval of Weeks 1-13 was decreased ($p \leq 0.01$) at 2000 ppm in males (↓8%) and females (↓12%). Transient differences in food consumption were noted sporadically in the other dose groups, but were not considered adverse.

TABLE 3. Mean food consumption (g/rat/day) at selected intervals in rats treated with flutriafol in the diet for up to 2 years. [a]

Week(s)	Dose (ppm)			
	0	20	200	2000
Males				
1	21.7	22.4	22.0	16.6** (↓24)
44	27.0	26.9	27.3	25.8* (↓4)
FC (1-13)	2479	2503	2509	2270** (↓8)
Females				
2	19.6	19.3	19.6	18.4** (↓6)
88	22.6	20.3* (↓10)	20.1* (↓11)	17.3** (↓23)
FC (1-13)	1841	1816	1825	1629** (↓12)

a Data were obtained from Tables 8-9 on pages 57-62 of MRID 47090352. Standard deviations were not reported. Percent difference from controls, calculated by reviewers, is included in parentheses.
* Significantly different ($p \leq 0.05$) from the control groups
** Significantly different ($p \leq 0.01$) from the control groups

2. **Compound consumption:** The mean achieved dosages were calculated to be, 0, 1.02, 10.0, and 102 mg/kg bw/day in males; and 0, 1.27, 12.2 and 122 mg/kg bw/day in females .

3. **Food utilization:** Food utilization (g food/g growth) was increased ($p \leq 0.01$) during the interval of Weeks 1-4 in the 2000 ppm males (↑8%) and females (↑11%). Food utilization during the interval of Weeks 1-12 was also increased in the 2000 ppm group (↑7% in each sex). Food utilization was similar or improved in the other dose groups compared to controls.

D. OPHTHALMOSCOPIC EXAMINATION: An increased incidence of retinal palor was noted in the 2000 ppm group at the interim sacrifice (3/20, each treated sex vs 0/20 controls) and terminal sacrifice (6/18 treated males vs 1/18 controls and 5/18 treated females vs 0/14 controls). The historical control range for 6 studies performed from 1979-1984 (# animals tested/study not reported) was 1-4 males and 0-3 females with retinal pallor. Severity was graded slightly pale/pale in all animals except that one 2000 ppm female at the interim sacrifice was graded as very pale. The incidences of other lesions were similar to controls. In particular, no co-existing abnormalities in the retinal vessels or hyper-reflection of the retina were observed. In addition, full histopathological investigation failed to reveal any evidence of retinal damage, which is typical in chemically induced retinal pallor. Therefore, this finding was considered incidental and age-related.

E. BLOOD ANALYSES

1. **Hematology:** A slight treatment-related anemia was noted in the 2000 ppm group as indicated by the following decreases ($p \leq 0.05$) in hematological parameters: (i) hemoglobin in males (↓4-7%) during Weeks 4-65 and females (↓4-9%) during Weeks 13-52, 78, and 92; (ii) hematocrit in males (↓3-8%) during Weeks 26-65 and females (↓5-11%) during Weeks 13-52, 78, and 104; (iii) mean cell volume in males (↓3-8%) during Weeks 4-104 and females (↓2-10%) during Weeks 4-104; and (iv) mean cell hemoglobin in males (↓4-7%) during Weeks 4, 26, 39, and 78-104 and females (↓4-10%) during Weeks 4-52 and 78-104. There were no significant differences in the erythrocyte count at ant time point for treated males and females, except for a slight (4%) increase in females in the 2000 ppm group at Week 4. There were no differences in the total serum iron and iron binding capacity of the treated animals compared to the controls, except that the total iron binding capacity of the 2000 ppm females was increased ($p \leq 0.01$) by 40%. The anemia was not considered to be an adverse effect due to the minor decreases in magnitude without corroborating clinical signs to corroborate an adverse condition. Increased ($p \leq 0.05$) lymphocytes were observed in the 2000 ppm females (↑22-61%) during Weeks 26-78 and 104, and increased ($p \leq 0.05$) total leukocytes were noted at Weeks 26, 39, and 78 (↑20-38%). The levels of increases in these parameters were not considered biologically adverse. Other differences ($p \leq 0.05$) were transient, minor, sporadic, and/or unrelated to dose.

TABLE 4. Hematological changes in male rats [a]

Week	Dose (ppm)			
	Males			
	0	20	200	2000
Males				
Hemoglobin (g/dL)				
4	14.7	14.6	14.7	13.7** (↓7)
13	14.6	14.6	14.5	13.8** (↓5)
26	15.8	15.8	15.9	15.1** (↓4)
52	16.4	16.5	16.4	15.6** (↓5)
104				
Hematocrit				
4	0.429	0.429	0.431	0.419
13	0.463	0.459	0.463	0441
26	0.479	0.479	0.481	0.463* (↓3)
52	0.476	0.489	0.475	0.443*8 (↓4)
104	0.422	0.384	0.391	0.383
MCV (fl)				
4	57.2	56.0* (↓2)	56.5	55.5** (↓3)
13	50.3	49.7	49.3	49.0* (↓3)
26	54.8	54.9	54.1	53.0** (↓3)
52	55.3	56.0	54.7	52.5** (↓5)
104	58.1	58.5	56.1	53.4** (↓8)
MCH (pg)				
4	19.6	19.1	19.2	18.6** (↓5)
13	16.0	15.8	15.6	15.4
26	18.1	18.1	17.8	17.3**(↓4)
52	19.1	19.3	18.8	18.5
104	18.5	18.8	18.0	17.2** (↓7)

Data obtained from pages 93, 95, 97, 99, 101 and 103 of MRID 47090352.

[a] Standard deviations were not reported; values in parentheses are percent difference from control, calculated by the reviewer.
*Significantly different ($p \leq 0.05$) from the control.
**Significantly different ($p \leq 0.01$) from the control.

TABLE 5. Hematological changes in female rats [a]

Week	Dose (ppm)			
	0	20	200	2000
Hemoglobin (g/dL)				
4	15.0	15.2	15.5	14.9
13	14.6	14.2	14.5	13.8** (↓5)
26	15.9	16.2* (↑2)	16.8	14.9** (↓6)
52	16.4	16.1	16.3	15.0** (↓8)
104	14.0	14.2	14.6	12.6
Hematocrit (g/100 g bw)				
4	0.447	0.450	0.462* (↑3)	0.453
13	0.473	0.465	0.474	0.451* (↓5)
26	0.474	0.476	0.475	0.449** (↓5)
52	0.463	0.451	0.458	0.423** (↓9)
104	0.437	0.437	0.454	0.389* (↓11)
MCV (fl)				
4	57.3	57.3	58.0	56.1** (↓2)
13	53.9	53.8	54.3	52.0** (↓4)
26	58.8	58.8	59.4	55.3** (↓6)
52	58.9	59.3	59.5	53.9** (↓8)
104	61.7	61.0	60.4	55.3** (↓10)
MCH (pg)				
4	19.3	19.4	19.4	18.5** (↓4)
13	16.6	16.5	16.7	15.9* (↓4)
26	19.7	20.0	20.1	18.4** (↓7)
52	20.9	21.1	21.2	19.1** (↓9)
104	19.8	19.8	19.4	17.8** (↓10)

Data obtained from pages 94, 96, 98, 100, 102 and 104 of MRID 47090352.
[a] Values are group means ± SD; values in parentheses are percent difference from control, calculated by the reviewer.
*Significantly different ($p \leq 0.05$) from the control.
**Significantly different ($p \leq 0.01$) from the control.

2. **Clinical chemistry:** At 2000 ppm, the following toxicologically significant differences ($p \leq 0.05$; unless otherwise stated) were observed: (i) increased plasma cholesterol in the females throughout the study (↑24-49%; NS at Week 91); (ii) decreased plasma triglycerides in the males during Weeks 4-65 (↓40-68%); (iii) decreased alkaline phosphatase in the males during Weeks 13-91 (↓12-33%); (iv) increased plasma total protein in the females throughout treatment (↑4-9%); and (v) increased plasma alanine transaminase during Weeks 4 and 13 (↑54-82%). Other differences ($p \leq 0.05$) were transient, minor, sporadic, and/or unrelated to dose.

TABLE 5. Clinical chemistry changes in male rats [a]				
Week	Dose (ppm)			
	0	20	200	2000
Plasma Albumin (g/100mL)				
4	4.79	4.83	4.70	4.41** (↓8)
13	4.92	4.91	4.98	5.04
26	4.81	4.82	4.85	4.92
52	4.68	4.58	4.61	4.64
104	3.83	3.70	3.90	3.76
Plasma Total Protein (g/100 mL)				
4	6.62	6.62	6.52	6.60
13	7.13	7.18	7.22	7.52** (↑5)
26	7.19	7.22	7.17	7.47* (↑4)
52	7.41	7.36	7.24	7.42
104	6.77	6.70	6.88	6.94
Plasma Cholesterol (mg/100 mL)				
4	68.3	65.4	64.7	61.9
13	74.3	76.3	74.0	67.8
26	85.3	86.3	85.3	79.2
52	116.3	135.1	126.3	108.6
104	205.3	224.5	235.7	226.0
Plasma Alanine Transaminase (mμ/mL)				
4	49.4	53.7	46.4	89.7** (↑82)
13	48.3	51.9	50.1	74.3** (↑54)
26	58.6	58.3	64.3	64.0
52	76.9	64.7	67.9	67.9
104	55.2	63.6	49.4	56.4

Data obtained from pages 94, 96, 98, 100, 102 and 104 of MRID 47090352.

[a] Values are group means ± SD; values in parentheses are percent difference from control, calculated by the reviewer.

***Significantly different ($p \leq 0.05$) from the control.**

****Significantly different ($p \leq 0.01$) from the control.**

TABLE 5. Clinical chemistry changes in female rats [a]				
Week	Dose (ppm)			
	0	20	200	2000
Plasma Albumin (g/100 mL)				
4	4.81	4.83	4.82	4.66* (↓3)
13	5.19	5.23	5.24	5.47** (↑5)
26	5.47	5.42	5.53	5.81** (↑6)
52	5.69	5.77	5.71	5.79
104	5.05	4.63	4.98	5.04
Plasma Total Protein (g/100 mL)				
4	6.57	6.54	6.63	6.80** (↑4)
13	7.02	7.15	7.09	7.59** (↑8)
26	7.32	7.28	7.38	7.89** (↑8)
52	7.63	7.79	7.72	8.17** (↑7)
104	7.32	7.18	7.40	7.87** (↑8)
Plasma Cholesterol (mg/100 mL)				
4	71.2	71.3	67.3	88.3** (↑24)
13	72.4	77.8	75.6	95.8** (↑32)
26	82.1	83.4	82.2	106.3** (↑29)
52	98.2	104.2	99.8	137.2*8 (↑40)
104	136.9	175.4	141.6	204.5* (↑49)
Plasma Alanine Transaminase (mμ/mL)				
4	46.9	43.5	45.3	47.7
13	48.9	49.3	46.3	47.3
26	53.1	58.0	60.8	54.6
52	63.0	57.1	59.5	55.8
104	105.6	52.3** (↓50)	55.0** (↓53)	57.8** (↓45)

Data obtained from pages 94, 96, 98, 100, 102 and 104 of MRID 47090352.

[a] Values are group means ± SD; values in parentheses are percent difference from control, calculated by the reviewer.

***Significantly different ($p \leq 0.05$) from the control.**

****Significantly different ($p \leq 0.01$) from the control.**

F. **URINALYSIS:** Increased levels of urinary ketones were observed in the 2000 ppm males, particularly during the first year. This analysis was semiquantitative and individual data were not presented; thus, it was difficult to determine the degree of difference from control. There was no more than trace ketones found at 2000 ppm at Week 104, and no further evidence of toxicity was observed on the kidney or urinary system. Therefore, this finding was considered to be without toxicological significance. Other differences ($p \leq 0.05$) observed during urinalysis were transient, minor, sporadic, and/or unrelated to dose.

G. SACRIFICE AND PATHOLOGY

1. **Organ weights:** In the 2000 ppm group, increased ($p \leq 0.05$) liver weights, both absolute and adjusted for body weight, were observed after 1 year of treatment (↑11-37%) and after 2 years (↑27-34%, except similar to control for absolute liver weight of the females; Tables 4a and 4b). The absolute and adjusted liver weights were also increased (↑11-12%) in males in the 200 ppm group at 2 years. Other differences ($p \leq 0.05$) in organ weights were minor and/or without corroborating evidence of toxicity.

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TABLE 6a. Liver weights (g) in rats treated with flutriafol in the diet for 1 year.[a]					
Week(s)		Dose (ppm)			
		0	20	200	2000
Males					
Liver	Absolute	21.8	21.0	23.9	26.6* (↑22)
	Adjusted for BW	20.9	20.6	23.4	28.7** (↑37)
Females					
Liver	Absolute	13.1	12.6	13.6	14.5* (↑11)
	Adjusted for BW	12.5	12.5	12.9	16.0** (↑28)

a **Data were obtained from Table 68 on page 121 of MRID 47090352. Standard deviations were not reported. Percent difference from controls, calculated by reviewers, is included in parentheses.**
* **Significantly different (p≤0.05) from the control groups**
** **Significantly different (p≤0.01) from the control groups**

TABLE 6b. Liver weights (g) in rats treated with flutriafol in the diet for 2 years.[a]					
Week(s)		Dose (ppm)			
		0	20	200	2000
Males					
Liver	Absolute	19.8	20.9	22.0** (↑11)	25.7** (↑30)
	Adjusted for BW	19.5	20.7	21.9** (↑12)	26.2** (↑34)
Females					
Liver	Absolute	14.5	13.9	13.7	15.6
	Adjusted for BW	13.6	13.3	13.1	17.3** (↑27)

a **Data were obtained from Table 69 on page 124 of MRID 47090352. Standard deviations were not reported. Percent difference from controls, calculated by reviewers, is included in parentheses.**
** **Significantly different (p≤0.01) from the control groups**

2. **Gross pathology:** Macroscopic lesions were not tabulated. The Sponsor stated that the only treatment-related finding was hepatic enlargement, often coupled with the presence of numerous discolored foci, commonly noted in the 2000 ppm group. Small discolored foci were also commonly observed in the liver of the 200 ppm males. These liver findings were observed after 2 years of treatment, but not after 1 year of treatment. No further information was provided.

3. **Microscopic pathology**

a. **Non-neoplastic:** Tabulated data for neoplasia were excerpted from pages 163-179, 200, and 207 of the study report, and are included as an attachment to this DER. Selected non-neoplastic lesions are reported in Tables 5a and 5b. After 1 year of treatment (including intercurrent deaths), an increased incidence of fatty change in the liver was observed in the males at 200 ppm (21% treated vs 7% controls) and 2000 (93%) ppm. The severity was minimal in the controls and 200 ppm males, but was minimal to marked in the 2000 ppm males. Hepatic centrilobular hypertrophy was increased at 2000 ppm in males (71% treated vs 0% control; minimal to moderate severity) and females (31% treated vs 0% controls; minimal severity).

After 2 years of treatment (including intercurrent deaths after interim kill), the following histological lesions were increased in incidence: (i) minimal to severe fatty change in the liver of the ≥200 ppm males (54-96% treated vs 24% controls) and 2000 ppm females (65% treated vs 23% controls); (ii) foci of altered hepatocytes (clear cell) in the ≥200 ppm males (40-50% treated vs 18% controls); (iii) bile duct proliferation/cholangiolarfibrosis in the 2000 ppm females (67% treated vs 44% controls); and (iv) hemosiderin accumulation in Kupffer cells in the liver in the 2000 ppm females (55% treated vs 0% controls). Hepatic centrilobular hypertrophy was increased in the 2000 ppm group (6-8% treated vs 0% controls). Additionally, an increased incidence of foci of cortical macrophages in adrenal glands was observed in the 2000 ppm females (80% treated vs 25% controls); however, there was no corroborating evidence of toxicity in the adrenal gland, and this lesion alone was not considered adverse. One 2000 ppm male was reported to have severe liver necrosis.

All differences in incidence of other microscopic lesions at the terminal sacrifice were slight, unrelated to dose, or not corroborated by other clinical or pathological evidence.

TABLE 7a. Incidence (# affected/# examined (% affected)) of selected liver lesions in rats treated with flutriafol in the diet for up to 1 year. [a]

Lesion	Dose (ppm)			
	0	20	200	2000
Males				
Fatty change (total)	1/15 (7)	0/16 (0)	3/14 (21)	13/14 (93)
Minimal	1	0	3	5
Moderate	0	0	0	5
Marked	0	0	0	3
Centrilobular hypertrophy (total)	0/15 (0)	0/16 (0)	1/14 (7)	10/14 (71)
Minimal	0	0	1	6
Moderate	0	0	0	4
Females				
Centrilobular hypertrophy (total)	0/12 (0)	0/13 (0)	0/12 (0)	4/13 (31)
Minimal	0	0	0	4

a Data were obtained from Tables 70-71 on pages 126 and 131 of MRID 47090352.

TABLE 7b. Incidence (# affected/# examined (% affected)) of selected microscopic findings in rats treated with flutriafol in the diet for up to 2 years. [a]

Lesion		Dose (ppm) 0	20	200	2000
Males					
Liver	Fatty change (total)	12/49 (24)	11/48 (23)	27/50 (54)	48/50 (96)
	Minimal	8	6	14	12
	Moderate	1	5	10	23
	Marked	3	0	3	11
	Severe	0	0	0	2
	Foci of altered hepatocytes, clear cell (total)	9/49 (18)	13/48 (27)	25/50 (50)	20/50 (40)
	Centrilobular hypertrophy (total)	0/49 (0)	0/48 (0)	0/50 (0)	3/50 (6)
Females					
Liver	Fatty change (total)	12/52 (23)	15/51 (29)	14/52 (27)	33/51 (65)
	Minimal	7	8	8	20
	Moderate	2	1	2	7
	Marked	2	6	4	2
	Severe	1	0	0	4
	Bile duct proliferation/cholangiolarfibrosis (total)	23/52 (44)	27/51 (53)	22/52 (42)	34/51 (67)
	Hemosiderin accumulation in Kupffer cells (total)	0/52 (0)	0/51 (0)	0/52 (0)	28/51 (55)
	Centrilobular hypertrophy (total)	0/52 (0)	0/51 (0)	0/52 (0)	4/51 (8)
Adrenal glands	Foci of cortical macrophages (total)	13/52 (25)	8/51 (16)	12/52 (23)	40/50 (80)

a **Data were obtained from Tables 72-73 on pages 140, 142, 152, and 154 of MRID 47090352.**

b. **Neoplastic:** No treatment-related increases in neoplastic lesions were observed. A slight increase in fibromas was noted in the subcutaneous tissue (6/64 treated vs 3/64 controls) in the 2000 ppm males, but the effect did not seem dose-dependent. Increased incidences of other fibromas or other subcutaneous neoplasia were not observed. Consequently, this effect was considered incidental. At 2000 ppm, there were slight increases in incidence (# affected/64 exposed in treated vs controls) of hepatocellular adenoma in males (1 vs 0) and females (2 vs 0) and hepatocellular carcinoma in males (2 vs 0). In each of these cases, 1 more animal had the reported tumor in this test than in the 3 reported historical controls. These historical controls were performed in 1979, 1980, and 1981, and included 64, 64, and 72 animals, respectively. In studies conducted since this study (1982-1987), the incidences of adenomas and carcinomas were 0-6.7% and 0-5.8%, respectively. These tumors are relatively common in rodents; therefore, the slightly increased incidences over concurrent controls were considered incidental. An increased incidence of Leydig cell tumors in the testes was noted in the 2000 ppm males (7/64 treated vs 0/64 controls); however, this incidence was within historical controls (2/72-7/64).

III. DISCUSSION and CONCLUSIONS

A. **INVESTIGATORS' CONCLUSIONS:** Increased liver weights and increased incidences of hepatic fatty change and clear cell foci of hepatocytes were noted in the 200 and 2000 ppm males. The following indications of toxicity were noted at 2000 ppm: (i) decreased body weight gain and food consumption in both sexes; (ii) increased liver weight and increased

incidence of hepatic fatty change in the females; (iii) changes in clinical chemistry in both sexes, considered to relate to the decreased growth rate and to the liver toxicity; and (iv) slight microcytic anemia in both sexes. There was no increase in neoplasia.

B. REVIEWER COMMENTS: No treatment-related effects were observed on mortality, ophthalmology, hematology, clinical chemistry, or urinalysis.

At ≥200 ppm, hepatotoxicity was noted in males. The absolute and adjusted liver weights were also increased (↑11-12%) in males in the 200 ppm group at 2 years. Small discolored foci were also commonly observed in the liver of the 200 ppm males. After 1 year of treatment, an increased incidence of fatty change in the liver was observed in the males at 200 (21% treated vs 7% controls) and 2000 (93%) ppm. The severity was minimal in the controls and 200 ppm males, but was minimal to marked in the 2000 ppm males. After 2 years of treatment, the following histological lesions were increased in incidence: minimal to severe fatty change in the liver of the ≥200 ppm males (54-96% treated vs 24% controls); and foci of altered hepatocytes (clear cell) in the ≥200 ppm males (40-50% treated vs 18% controls).

A slight treatment-related anemia was noted in the 2000 ppm group as indicated by the following decreases ($p \leq 0.05$) in hematological parameters: (i) hemoglobin in males (↓4-7%) during Weeks 4-65 and females (↓4-9%) during Weeks 13-52, 78, and 92; (ii) hematocrit in males (↓3-8%) during Weeks 26-65 and females (↓5-11%) during Weeks 13-52, 78, and 104; (iii) mean cell volume in males (↓3-8%) during Weeks 4-104 and females (↓2-10%) during Weeks 4-104; and (iv) mean cell hemoglobin in males (↓4-7%) during Weeks 4, 26, 39, and 78-104 and females (↓4-10%) during Weeks 4-52 and 78-104. The total iron binding capacity of the 2000 ppm females was increased ($p \leq 0.01$) by 40%. Increased ($p \leq 0.05$) lymphocytes were observed in the 2000 ppm females (↑22-61%) during Weeks 26-78 and 104, and increased ($p \leq 0.05$) total leukocytes were noted at Weeks 26, 39, and 78 (↑20-38%). The hematological changes were not considered to be adverse effects due to the minor decreases in magnitude without corroborating clinical signs to corroborate an adverse condition.

At 2000 ppm, the following toxicologically significant differences ($p \leq 0.05$; unless otherwise stated) were observed: (i) increased plasma cholesterol in the females throughout the study (↑24-49%; NS at Week 91); (ii) decreased plasma triglycerides in the males during Weeks 4-65 (↓40-68%); (iii) decreased alkaline phosphatase in the males during Weeks 13-91 (↓12-33%); (iv) increased plasma total protein in the females throughout treatment (↑4-9%); and (v) increased plasma alanine transaminase during Weeks 4 and 13 (↑54-82%).

Additionally at 2000 ppm, hepatoxicity was noted in both sexes. In both sexes, increased ($p \leq 0.05$) liver weights, both absolute and adjusted for body weight, were observed after 1 year of treatment (↑11-37%) and after 2 years (↑27-34%, except for females who's absolute liver weight were similar to controls). The Sponsor stated that the only treatment-related gross finding was hepatic enlargement, often coupled with the presence of numerous discolored foci, commonly noted in both sexes. These liver findings were observed after 2 years of treatment, but not after 1 year of treatment. After 2 years of treatment, the following

histological hepatic lesions were increased in incidence in the females: (i) minimal to severe fatty change (65% treated vs 23% controls); (ii) bile duct proliferation/ cholangiolarfibrosis (67% treated vs 44% controls); (iii) hemosiderin accumulation in Kupffer cells (55% treated vs 0% controls); and (iv) centrilobular hypertrophy (8% treated vs 0% controls). Hepatic centrilobular hypertrophy was increased in incidence at the interim sacrifice in males (71%) and females (31%), but only minor increases were noted at terminal sacrifice in both sexes (6-8%) with 0% in the controls. Additionally, an increased incidence of foci of cortical macrophages in adrenal glands was observed in the 2000 ppm females (80% treated vs 25% controls); however, there was no corroborating evidence of toxicity in the adrenal gland, and this lesion alone was not considered adverse.

The LOAEL is 2000 ppm (102/122mg/kg bw/day in males/females), based on adverse liver effects (increased liver weights, fatty change, bile duct proliferation/cholangiolarfibrosis, hemosiderin accumulation in Kupffer cells and centrilobular hypertrophy), and clinical chemistry findings. The NOAEL is 200 ppm (10.0/12.2 mg/kg bw/day in males/females).

At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls. Dosing was considered adequate based on decreased body weight gain and food consumption, increased food utilization, and hepatotoxicity observed in both sexes.

This study is classified as **Acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4300; OECD 453) for a combined chronic toxicity/carcinogenicity study in rats.

C **STUDY DEFICIENCIES:** The following minor deficiencies were observed. Note that this test was finished prior to the adoption of Pesticide Assessment Guidelines Subdivision F in November 1984:

- Standard deviations were not reported with the mean in the tabulated data.
- Concentrations of electrolytes, certain enzymes and creatinine in the blood were not determined.
- The urine appearance, volume, and blood content were not determined.
- Organ weights for the heart, spleen, epididymides, and uterus were not determined.
- Individual animal data were not presented.

ATTACHMENT

The following are pages 163 through 179, 200, and 207 of the study report.

FLUTRIAFOL: 2 YEAR FEEDING STUDY IN RATS
TABLE 75
INCIDENCE OF NEOPLASTIC FINDINGS IN INTERCURRENT ANIMALS UP TO INTERIM KILL

Tissue/Pathological Findings	Male				Female			
	Dietary Concentration of Flutriafol (ppm)							
	0	20	200	2000	0	20	200	2000
Number of animals examined	4	5	2	3	0	1	0	1
NERVOUS SYSTEM								
Brain Number examined	4	5	2	3	0	1	0	1
Astrocytoma	0	0	1	0	0	0	0	0
Spinal Cord Number examined	4	5	2	3	0	1	0	1
Ependymoma	0	0	0	0	0	1	0	0

FLUTRIAFOL: 2 YEAR FEEDING STUDY IN RATS
TABLE 76
INCIDENCE OF NEOPLASTIC FINDINGS IN INTERIM KILL ANIMALS

Tissue/Pathological Findings		Male				Female			
		Dietary Concentration of Flutriafol (ppm)							
		0	20	200	2000	0	20	200	2000
Number of animals examined		11	11	12	11	12	12	12	12
ALIMENTARY SYSTEM									
Liver	Number examined	11	11	12	11	12	12	12	12
Adenoma		0	0	0	0	0	0	0	1
ENDOCRINE SYSTEM									
Pituitary	Number examined	11	11	12	10	12	12	12	11
Adenoma		1	1	0	0	5	1	5	3
UROGENITAL SYSTEM									
Mammary Gland	Number examined	0	0	0	0	12	12	12	12
Fibroadenoma		0	0	0	0	0	0	1	0

FLUTRIAFOL: 2 YEAR FEEDING STUDY IN RATS
TABLE 77
INCIDENCE OF NEOPLASTIC FINDINGS IN INTERCURRENT ANIMALS FROM INTERIM TO TERMINAL KILL

Tissue/Pathological Findings		Male				Female			
		Dietary Concentration of Flutriafol (ppm)							
		0	20	200	2000	0	20	200	2000
Number of animals examined		26	25	24	26	33	28	27	22
ALIMENTARY SYSTEM									
Buccal Cavity/Hard Palate									
Squamous cell carcinoma		3	0	0	1	0	0	0	1
Keratotic papilloma		0	1	0	1	0	0	0	0
Stomach	Number examined	26	24	24	26	32	28	27	22
Fibrosarcoma		0	0	0	1	0	0	0	0
Ileum	Number examined	26	23	24	26	31	27	27	22
Leiomyoma		0	0	0	0	1	0	0	0
Colon	Number examined	26	23	24	26	32	27	26	22
Adenocarcinoma		0	0	0	0	0	0	0	1
Liver	Number examined	26	25	24	26	33	28	27	22
Hepatocellular carcinoma		0	0	0	1	0	0	0	0
Haemangiosarcoma		1	0	0	0	0	0	0	0
Exocrine pancreas	Number examined	26	25	24	26	32	28	27	22
Adenoma		0	0	0	1	0	0	0	0

FLUTRIAFOL: 2 YEAR FEEDING STUDY IN RATS
TABLE 77 - Continued
INCIDENCE OF NEOPLASTIC FINDINGS IN INTERCURRENT ANIMALS FROM INTERIM TO TERMINAL KILL

Tissue/Pathological Findings		Male				Female			
		Dietary Concentration of Flutriafol (ppm)							
		0	20	200	2000	0	20	200	2000
CARDIOVASCULAR SYSTEM									
Heart	Number examined	26	25	24	26	33	28	27	22
Malignant neurinoma		0	0	0	0	0	0	1	0
ENDOCRINE SYSTEM									
Adrenal	Number examined	26	25	24	26	33	28	27	22
Phaeochromocytoma		1	0	1	2	0	0	0	0
Cortical adenoma		0	1	0	0	0	0	1	0
Malignant ganglioneuroma		0	0	0	0	0	1	0	0
Endocrine pancreas	Number examined	26	25	24	26	32	28	27	22
Islet cell adenoma		0	0	0	0	0	0	1	0
Islet cell adenocarcinoma		0	0	0	1	0	0	0	0
Parathyroid	Number examined	23	23	17	25	25	25	26	16
Adenoma		0	0	0	0	0	0	1	0
Pituitary	Number examined	26	25	23	26	33	27	27	21
Adenoma		10	8	7	9	30	24	25	19
Schwannoma		0	1	0	1	0	0	0	0
Thyroid	Number examined	26	25	23	26	33	28	27	22
Parafollicular adenoma		0	0	0	1	0	0	1	0
Follicular adenoma		0	0	1	0	0	0	0	1
Follicular adenocarcinoma		0	0	0	0	1	0	0	0

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FLUTRIAFOL: 2 YEAR FEEDING STUDY IN RATS
TABLE 77 - Continued
INCIDENCE OF NEOPLASTIC FINDINGS IN INTERCURRENT ANIMALS FROM INTERIM TO TERMINAL KILL

Tissue/Pathological Findings	Male				Female			
	Dietary Concentration of Flutriafol (ppm)							
	0	20	200	2000	0	20	200	2000
HAEMOPOIETIC AND LYMPHORETICULAR SYSTEMS								
Spleen Number examined	26	25	24	26	33	28	27	22
Histiocytic lymphoma	0	0	1	0	0	1	0	0
Thymus Number examined	25	24	22	25	33	28	25	20
Squamous cell carcinoma	0	0	1	0	0	0	0	0
Lymphoma	0	1	0	0	0	0	1	0
Thymoma	0	0	1	0	0	0	0	0
Generalised lymphoma	1	2	1	2	1	0	0	0
INTEGUMENT AND SUBCUTANEOUS TISSUES								
Skin Number examined	26	25	24	25	33	28	27	21
Keratoacanthoma	1	0	0	0	0	0	0	0
Squamous cell carcinoma	0	1	0	0	0	0	0	0
Keratotic papilloma	0	1	0	1	0	0	0	0
Subcutaneous tissues Number examined	26	25	24	25	33	28	27	21
Haemangioma	1	0	0	0	0	0	0	0
Haemangiosarcoma	1	0	0	0	1	0	0	0
Fibroma	3	0	1	4	0	1	1	1
Fibrosarcoma	2	0	1	0	0	0	0	0

FLUTRIAFOL: 2 YEAR FEEDING STUDY IN RATS
TABLE 77 - Continued
INCIDENCE OF NEOPLASTIC FINDINGS IN INTERCURRENT ANIMALS FROM INTERIM TO TERIMINAL KILL

Tissue/Pathological Findings	Male				Female			
	Dietary Concentration of Flutriafol (ppm)							
	0	20	200	2000	0	20	200	2000
INTEGUMENT AND SUBCUTANEOUS TISSUES - CONTINUED								
Subcutaneous tissues - continued								
Lipoma	2	0	1	2	0	0	0	0
Anaplastic sarcoma	0	0	0	1	0	0	0	0
Basal cell epithelioma	0	0	0	0	1	0	0	0
MUSCULO-SKELETAL SYSTEM								
Bone Number examined	26	25	24	26	33	28	27	22
Osteosarcoma	0	1	0	0	0	0	0	0
NERVOUS SYSTEM/SPECIAL SENSE ORGANS								
Brain Number examined	26	25	24	26	33	28	27	22
Astrocytoma	1	4	2	2	1	1	1	0
Meningioma	0	1	0	1	1	0	0	0
Glioblastoma	0	0	0	0	1	0	0	0
UROGENITAL SYSTEM								
Kidney Number examined	26	25	24	26	33	28	27	22
Cortical adenoma	1	0	0	0	0	0	0	0

FLUTRIAFOL: 2 YEAR FEEDING STUDY IN RATS
TABLE 77 - Continued
INCIDENCE OF NEOPLASTIC FINDINGS IN INTERCURRENT ANIMALS FROM INTERIM TO TERMINAL KILL

Tissue/Pathological Findings	Male				Female			
	Dietary Concentration of Flutriafol (ppm)							
	0	20	200	2000	0	20	200	2000
UROGENITAL SYSTEM - CONTINUED								
Testis/Epididymis Number examined	26	25	24	26	-	-	-	-
Leydig cell tumour	0	0	1	2	-	-	-	-
Mesothelioma	1	1	2	0	-	-	-	-
Ovary Number examined	-	-	-	-	33	28	27	22
Granulosa theca cell tumour	-	-	-	-	0	1	0	0
Uterus/Cervix Number examined	-	-	-	-	33	28	27	22
Focal endometrial hyperplasia/carcinoma in situ	-	-	-	-	0	1	0	0
Adenocarcinoma	-	-	-	-	0	1	0	1
Fibrosarcoma	-	-	-	-	0	0	1	1
Leiomyosarcoma	-	-	-	-	0	0	1	0
Stromal cell sarcoma	-	-	-	-	0	0	1	0
Endometrial stromal polyp	-	-	-	-	1	2	2	0
Mammary Gland Number examined	0	0	0	1	33	28	27	22
Fibroadenoma	0	0	0	0	4	5	4	1
Adenocarcinoma	0	0	0	0	4	3	5	2
MISCELLANEOUS TISSUE								
Abdominal Cavity								
Cystic adenocarcinoma	0	0	0	0	1	0	0	0

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FLUTRIAFOL: 2 YEAR FEEDING STUDY IN RATS
TABLE 78
INCIDENCE OF NEOPLASTIC FINDINGS IN ANIMALS KILLED AT TERMINATION

Tissue/Pathological Findings		Male				Female			
		Dietary Concentration of Flutriafol (ppm)							
		0	20	200	2000	0	20	200	2000
Number of animals examined		23	23	26	24	19	23	25	29
ALIMENTARY SYSTEM									
Liver	Number examined	23	23	26	24	19	23	25	29
Hepatocellular adenoma		0	0	0	1	0	0	0	1
Hepatocellular carcinoma		0	0	1	1	0	0	0	0
ENDOCRINE SYSTEM									
Adrenal	Number examined	23	23	26	24	19	23	25	28
Phaeochromocytoma		0	0	1	0	0	0	0	0
Cortical adenoma		0	0	0	1	1	2	0	0
Endocrine Pancreas	Number examined	23	23	26	24	19	23	25	29
Islet cell adenoma		0	0	0	1	0	0	0	0
Pituitary	Number examined	22	21	24	24	19	23	25	29
Adenoma		9	6	12	11	18	16	21	22
Thyroid	Number examined	23	23	26	24	19	23	25	29
Parafollicular adenoma		1	3	0	1	0	0	1	0
Follicular adenoma		0	0	0	0	0	1	0	0
Parafollicular carcinoma		0	1	0	0	0	0	0	0

FLUTRIAFOL: 2 YEAR FEEDING STUDY IN RATS
TABLE 78 - Continued
INCIDENCE OF NEOPLASTIC FINDINGS IN ANIMALS KILLED AT TERMINATION

Tissue/Pathological Findings		Male				Female			
		Dietary Concentration of Flutriafol (ppm)							
		0	20	200	2000	0	20	200	2000
HAEMOPOIETIC AND LYMPHORETICULAR SYSTEMS									
Mesenteric lymph node	Number examined	23	23	26	24	19	23	24	29
Histiocytoma		0	0	1	0	0	0	0	0
Spleen	Number examined	23	23	26	24	19	23	25	29
Histiocytic lymphoma		0	0	1	0	0	0	0	0
INTEGUMENT AND SUBCUTANEOUS TISSUES									
Skin	Number examined	23	23	26	24	19	23	25	29
Fibroma		0	1	0	0	0	0	0	0
Subcutaneous tissue	Number examined	23	23	26	24	19	23	25	29
Fibroma		0	2	0	2	0	0	0	0
Fibrosarcoma		1	0	0	0	0	0	0	0
Lipoma		1	0	1	0	0	0	0	0
NERVOUS SYSTEM/SPECIAL SENSE ORGANS									
Brain	Number examined	23	23	26	24	19	23	25	29
Astrocytoma		0	0	0	0	1	0	1	0
Meningioma		0	1	0	0	0	0	0	0

FLUTRIAFOL: 2 YEAR FEEDING STUDY IN RATS
TABLE 78 - Continued
INCIDENCE OF NEOPLASTIC FINDINGS IN ANIMALS KILLED AT TERMINATION

Tissue/Pathological Findings		Male				Female			
		Dietary Concentration of Flutriafol (ppm)							
		0	20	200	2000	0	20	200	2000
RESPIRATORY SYSTEM									
Lung	Number examined	23	23	26	24	19	23	25	29
Squamous cell carcinoma		0	0	0	0	0	0	1	0
UROGENITAL SYSTEM									
Testis/Epididymis	Number examined	23	23	26	24	-	-	-	-
Leydig cell tumour		0	4	2	5	-	-	-	-
Mesothelioma		1	0	0	0	-	-	-	-
Ovary	Number examined	-	-	-	-	19	23	25	29
Granulosa theca cell tumour		-	-	-	-	0	1	1*	0
Uterus/Cervix	Number examined	-	-	-	-	19	23	25	29
Focal endometrial hyperplasia/carcinoma in situ		-	-	-	-	0	0	0	1
Adenocarcinoma		-	-	-	-	1	1	0	2
Leiomyoma		-	-	-	-	0	0	0	1
Endometrial stromal polyp		-	-	-	-	0	2	3	3
Mammary Gland	Number examined	3	2	1	2	19	23	25	29
Fibroadenoma		0	0	0	0	0	2	1	0
Adenocarcinoma		0	0	0	0	2	1	0	0

* malignant

FLUTRIAFOL: 2 YEAR FEEDING STUDY IN RATS
TABLE 79
INCIDENCE OF NEOPLASTIC FINDINGS IN ALL ANIMALS

Tissue/Pathological Findings		Male				Female			
		Dietary Concentration of Flutriafol (ppm)							
		0	20	200	2000	0	20	200	2000
Number of Animals examined		64	64	64	64	64	64	64	64
ALIMENTARY SYSTEM									
Buccal cavity/Hard palate									
Squamous cell carcinoma		3	0	0	1	0	0	0	1
Keratotic papilloma		0	1	0	1	0	0	0	0
Stomach	Number examined	63	63	64	64	63	64	64	64
Fibrosarcoma		0	0	0	1	0	0	0	0
Ileum	Number examined	64	62	63	64	63	63	64	64
Leiomyoma		0	0	0	0	1	0	0	0
Colon	Number examined	64	62	64	64	61	63	63	63
Adenocarcinoma		0	0	0	0	0	0	0	1
Liver	Number examined	HC 64	64	64	64	HC 64	64	64	64
Hepatocellular adenoma		0 0	0	0	1	0-1 0	0	0	2
Hepatocelluar carcinoma		0-1 0	0	1	2	0 0	0	0	0
Haemangiosarcoma		1	0	0	0	0	0	0	0
Exocrine pancreas	Number examined	64	64	64	64	64	64	64	64
Adenoma		0	0	0	1	0	0	0	0

FLUTRIAFOL: 2 YEAR FEEDING STUDY IN RATS
TABLE 79 - Continued
INCIDENCE OF NEOPLASTIC FINDINGS IN ALL ANIMALS

Tissue/Pathological Findings		Male				Female			
		Dietary Concentration of Flutriafol (ppm)							
		0	20	200	2000	0	20	200	2000
CARDIOVASCULAR SYSTEM									
Heart	Number examined	64	64	64	64	64	64	64	64
Malignant neurinoma		0	0	0	0	0	0	1	0
ENDOCRINE SYSTEM									
Adrenal	Number examined	64	64	64	64	64	64	64	63
Phaeochromocytoma		1	0	2	2	0	0	0	0
Cortical adenoma		0	1	0	1	1	2	1	0
Malignant ganglioneuroma		0	0	0	0	0	1	0	0
Endocrine pancreas	Number examined	64	64	64	64	64	64	64	64
Islet cell adenoma		0	0	0	1	0	0	1	0
Islet cell adenocarcinoma	-	0	0	0	1	0	0	0	0
Parathyroid	Number examined	54	58	53	58	45	56	56	50
Adenoma		0	0	0	0	0	0	1	0
Pituitary	Number examined	63	62	61	63	64	63	64	62
Adenoma		20	15	19	20	53	41	51	45
Schwannoma		0	1	0	1	0	0	0	0

FLUTRIAFOL: 2 YEAR FEEDING STUDY IN RATS
TABLE 79 - Continued
INCIDENCE OF NEOPLASTIC FINDINGS IN ALL ANIMALS

Tissue/Pathological Findings		Male				Female			
		Dietary Concentration of Flutriafol (ppm)							
		0	20	200	2000	0	20	200	2000
ENDOCRINE SYSTEM - CONTINUED									
Thyroid	Number examined	64	64	63	64	64	64	64	64
Parafollicular adenoma		1	3	0	2	0	0	2	0
Parafollicular carcinoma		0	1	0	0	0	0	0	0
Follicular adenoma		0	0	1	0	0	1	0	1
Follicular adenocarcinoma		0	0	0	0	1	0	0	0
HAEMOPOIETIC AND LYMPHORETICULAR SYSTEMS									
Mesenteric lymph node	Number examined	63	63	63	64	64	63	63	64
Histiocytoma		0	0	1	0	0	0	0	0
Spleen	Number examined	64	64	64	64	64	64	64	64
Histiocytic lymphoma		0	0	2	0	0	1	0	0
Thymus	Number examined	62	62	62	61	64	64	62	62
Squamous cell carcinoma		0	0	1	0	0	0	0	0
Lymphoma		0	1	0	0	0	0	1	0
Thymoma		0	0	1	0	0	0	0	0
Generalised lymphoma		1	2	1	2	1	0	0	0

FLUTRIAFOL: 2 YEAR FEEDING STUDY IN RATS
TABLE 79 - Continued
INCIDENCE OF NEOPLASTIC FINDINGS IN ALL ANIMALS

Tissue/Pathological Findings	Male				Female			
	Dietary Concentration of Flutriafol (ppm)							
	0	20	200	2000	0	20	200	2000
INTEGUMENT AND SUBCUTANEOUS TISSUES								
Skin Number examined	64	64	64	63	64	64	64	63
Keratoacanthoma	1	0	0	0	0	0	0	0
Squamous cell carcinoma	0	1	0	0	0	0	0	0
Keratotic papilloma	0	1	0	1	0	0	0	0
Fibroma	0	1	0	0	0	0	0	0
Subcutaneous tissue Number examined	64	64	64	64	64	64	64	64
Haemangioma	1	0	0	0	0	0	0	0
Haemangiosarcoma	1	0	0	0	1	0	0	0
Fibroma Incidental, within HC?	3 5%	2	1	6 9%	0	1	1	1
Fibrosarcoma	3	0	1	0	0	0	0	0
Lipoma	3	0	2	2	0	0	0	0
Anaplastic sarcoma	0	0	0	1	0	0	0	0
Basal cell epithelioma	0	0	0	0	1	0	0	0
MUSCULO SKELETAL SYSTEM								
Bone Number examined	64	64	64	64	64	64	64	64
Osteosarcoma	0	1	0	0	0	0	0	0

FLUTRIAFOL: 2 YEAR FEEDING STUDY IN RATS
TABLE 79 - Continued
INCIDENCE OF NEOPLASTIC FINDINGS IN ALL ANIMALS

Tissue/Pathological Findings		Male				Female			
		Dietary Concentration of Flutriafol (ppm)							
		0	20	200	2000	0	20	200	2000
NERVOUS SYSTEM/SPECIAL SENSES									
Brain	Number examined	64	64	64	64	64	64	64	64
Astrocytoma		1	4	3	2	2	1	2	0
Meningioma		0	2	0	1	1	0	0	0
Glioblastoma		0	0	0	0	1	0	0	0
Spinal cord	Number examined	64	64	64	64	64	64	64	64
Ependymoma		0	0	0	0	0	1	0	0
RESPIRATORY SYSTEM									
Lung	Number examined	64	64	64	64	64	64	64	64
Squamous cell carcinoma		0	0	0	0	0	0	1	0
UROGENITAL SYSTEM									
Kidney	Number examined	64	64	64	64	64	64	64	64
Cortical adenoma		1	0	0	0	0	0	0	0
Testis/Epididymis	Number examined	64	64	64	64	-	-	-	-
Leydig cell tumour		0	4	3	7	-	-	-	-
Mesothelioma		2	1	2	0	-	-	-	-

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FLUTRIAFOL: 2 YEAR FEEDING STUDY IN RATS
TABLE 79 - Continued
INCIDENCE OF NEOPLASTIC FINDINGS IN ALL ANIMALS

Tissue/Pathological Findings	Male				Female			
	Dietary Concentration of Flutriafol (ppm)							
	0	20	200	2000	0	20	200	2000
UROGENITAL SYSTEM - CONTINUED								
Ovary Number examined	-	-	-	-	64	64	64	64
Granulosa/theca cell tumour	-	-	-	-	0	2	1*	0
Uterus/Cervix Number examined	-	-	-	-	64	64	64	64
Focal endometrial hyperplasia/carcinoma in situ	-	-	-	-	0	1	0	1
Adenocarcinoma	-	-	-	-	1	2	0	3
Fibrosarcoma	-	-	-	-	0	0	1	1
Leiomyoma	-	-	-	-	0	0	0	1
Leiomyosarcoma	-	-	-	-	0	0	1	0
Stromal cell sarcoma	-	-	-	-	0	0	1	0
Endometrial stromal polyp	-	-	-	-	1	4	5	3
Mammary gland Number examined	3	2	1	3	64	64	64	64
Fibroadenoma	0	0	0	0	4	7	6	1
Adenocarcinoma	0	0	0	0	6	4	5	2
MISCELLANEOUS TISSUES								
Abdominal cavity								
Cystic adenocarcinoma	0	0	0	0	1	0	0	0

*Malignant

FLUTRIAFOL: 2 YEAR FEEDING STUDY IN RATS
TABLE 80
INCIDENCE OF ANIMALS WITH NEOPLASMS

Incidence Categogory	Male				Female			
	Dietary Concentration of Flutriafol (ppm)							
	0	20	200	2000	0	20	200	2000
Number of animals with neoplasms	32	30	34	40	55	50	56	51
Number of animals with benign neoplasms	25	24	28	36	53	47	53	48
Number of animals with malignant neoplasms	11	10	10	12	14	11	12	9
Number of animals with single neoplasms	23	21	27	25	39	33	37	40
Number of animals with multiple neoplasms of different types	9	9	7	15	15	17	19	11
Number of animals with multiple benign neoplasms of different types	5	7	3	9	7	11	13	5
Number of animals with multiple malignant neoplasms of different types	0	0	0	0	1	0	2	0
Total Number of Animals	64	64	64	64	64	64	64	64

APPENDIX B

INCIDENCE OF INTERSTITIAL (LEYDIG) CELL TUMOURS OF THE TESTIS IN CONTROL ALDERLEY PARK RATS FROM RECENT TWO YEAR FEEDING STUDIES AT IMPERIAL CHEMICAL INDUSTRIES PLC, CENTRAL TOXICOLOGY LABORATORY

Report Reference Number	Start Date	Duration Weeks	Number of Male Rats Examined	Incidence
CTL/P/669	March 1979	105	64	7
CTL/P/863	August 1980	106	64	2
CTL/P/980	January 1981	105	72	2

INCIDENCE OF HEPATOCELLULAR LIVER TUMOURS IN CONTROL ALDERLEY PARK RATS FROM RECENT TWO YEAR FEEDING STUDIES AT IMPERIAL CHEMICAL INDUSTRIES PLC, CENTRAL TOXICOLOGY LABORATORY

Report Reference Number	Start Date	Duration Weeks	Number of Rats Per Group		Incidence of:			
			Males (M)	Females (F)	Adenoma M	Adenoma F	Carcinoma M	Carcinoma F
CTL/P/669	May 1979	105	64	64	0	0	1	0
CTL/P/863	July 1980	106	64	64	0	0	0	0
CTL/P/980	January 1981	105	72	72	0	1	0	0

FIRST SUPPLEMENT TO
FLUTRIAFOL: 2 YEAR FEEDING STUDY IN RATS

TABLE A

INCIDENCES OF HEPATOCELLULAR TUMOURS IN MALE Alpk:APfSD RATS
(DATA EXCLUDE ANIMALS SCHEDULED FOR INTERIM KILL)

Study Start	Adenoma		Carcinoma+		Combined	
	Number	%	Number	%	Number	%
May 1979	0/104	0.0	1/104	1.0	1/104	1.0
July 1980	0/ 52	0.0	0/ 52	0.0	0/ 52	0.0
January 1981	0/ 62	0.0	0/ 62	0.0	0/ 62	0.0
DIET CHANGE*						
November 1982 FLUTRIAFOL	0/ 52	0.0	0/ 52	0.0	0/ 52	0.0
October 1983	0/ 64	0.0	1/ 64	1.6	1/ 64	1.6
February 1984	7/104	6.7	2/104	1.9	9/104	8.7
October 1984	0/ 52	0.0	1/ 52	1.9	1/ 52	1.9
February 1985	0/ 52	0.0	3/ 52	5.8	3/ 52	5.8
Aug/Sept 1985	0/ 52	0.0	3/ 52	5.8	3/ 52	5.8
October 1986	1/ 52	1.9	0/ 52	0.0	1/ 52	1.9
March 1987	3/ 52	5.8	2/ 52	3.8	5/ 52	9.6
November 1987	1/ 52	1.9	0/ 52	0.0	1/ 52	1.9
(2000ppm FLUTRIAFOL	1/ 52	1.9	2/ 52	3.8	3/ 52	5.7

*See previous page for details.

+Includes adenocarcinoma.